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Dopamine Polymorphisms and Depressive Symptoms Predict Foods Intake: Results from a Nationally Representative Sample

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Abstract

Depression and variation in dopamine related genes have both independently been associated with food consumption. Depressive symptoms could synergistically interact with genetic variation to influence food intake. We examined the interaction between high depressive symptoms and functional polymorphisms of dopamine transporter (SLC6A3), monoamine oxidase A (MAOA), dopamine receptor D2 (DRD2) and dopamine receptor D4 (DRD4) on intake of high-calorie sweet, high-calorie non-sweet, and low-calorie foods in the National Longitudinal Study of Adolescent Health (Add Health). Multivariate linear regression analyses were used to examine main effects of gene and depression symptoms and their interaction (genotype-by-high depression symptoms) on food categories. Applying a false discovery rate criterion for multiple comparisons indicated a statistically significant interaction for females with high depressive symptoms and the SLC6A3 gene, such that those with the SLC6A3 10/10 allele reported greater intake of high-calorie sweet foods than their counterparts high in depressive symptoms with the SLC6A3 any 9 allele (LS mean 10/10 allele = 2.5, SE = .13; LS mean any 9 allele = 1.8, SE = .13, $p < .05$). These findings highlight that the relationship between depression and food intake may vary as a function of genetic polymorphism. Further research is needed to confirm these findings.

Keywords

Adolescent; Diet; Dopamine; Depression

INTRODUCTION

A depressive episode is characterized by depressed mood and a loss of interest in pleasurable activities. Clinical depression and depressive symptoms, for some, are also associated with a marked change in appetite, which can involve either a reduced interest in food or an increased appetite and craving for sweets and other carbohydrates (American Psychiatric Association [DSM-IV-TR], 2000). The degree to which depressive symptoms, among individuals in the general population, is associated with intake of unhealthy energy-dense foods has been the subject of an increasing body of research because knowledge of such associations could inform more individually tailored treatment and prevention approaches that target healthier dietary intake.

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Recent studies in adults have document an association between depressive symptoms, increased consumption of high calorie foods (e.g., sweets, fast foods) and reduced consumption of fruits and vegetables (Jeffery et al., 2009; Kontinen, Mannisto, Sarlio-Lahteenkorva, Silventoinen, & Haukkala, 2010; Mikolajczyk, El Ansari, & Maxwell, 2009). However, less is known about the extent to which depressive symptoms are associated with diet quality during adolescence; a developmental period when both unhealthy eating practices and depressive symptoms are more common. An exception is a study of middle and high school students from the Project EAT (Eating Among Teens) cohort, in which investigators found that teens with higher depressive symptoms reported slightly higher percent calories from fat, greater daily servings of soft drinks, and more sucrose intake. These trends were more pronounced among males in their sample. (Fulkerson, Sherwood, Perry, Neumark-Sztainer, & Story, 2004). Similarly, a study of an Australian adolescent cohort (10 to 14 years of age) reported a linear cross-sectional association between greater depressive symptoms and poorer diet quality (i.e., high energy intake of nutrient-poor foods) (Jacka et al., 2010).

Another factor that may drive food intake and a predilection for certain types of food is an individual's susceptibility to the rewarding or motivational value of food. Certain types of foods, especially sugars and fats, are powerful rewards that can promote non-homeostatic eating. A key neurotransmitter that underlies the modulation of the rewarding properties of food (as well as other substances) is dopamine (DA), which it does through its projections from the ventral tegmental area to the nucleus accumbens. Brain imaging studies have found that obese individuals, compared to their healthy weight counterparts, show hyper-responsivity in certain reward and learning regions in response to food cues, have reduced dopamine D₂ receptor availability, and demonstrate less activation in reward/learning regions during consumption of palatable foods (Stice, Spoor, Bohon, & Small, 2008). These findings have led some to hypothesize that individuals who excessively consume highly palatable foods may be doing so to compensate for a reward deficiency related to aberrant dopamine functioning and availability (Volkow, Wang, & Baler, 2011). Notably, the dopaminergic system is also associated with regulation of mood and affect, and deficient dopaminergic transmission is thought to play a role in major depressive disorder and in depressive mood generally (Opmeer, Kortekaas, & Aleman, 2010). The reward deficiency hypothesis of depression proposes that Individuals who are experiencing chronic high levels of depressive symptoms receive less enjoyment from rewarding stimuli. The high comorbidity of smoking and other substance use problems (and potentially symptoms of hyperphagia) may indicate compensatory behavior resulting from aberrant dopamine functioning and availability (Audrain-McGovern, Lerman, Wileyto, Rodriguez, & Shields, 2004; Lerman et al., 1998; Spring, Pingitore, & McChargue, 2003).

There are a number of genes that have been linked with neurotransmission of dopamine, some which have been the subject of candidate gene studies of both depression and food intake. These candidate gene studies have included dopamine receptor 2 (DRD2), dopamine receptor 4 (DRD4), and solute carrier family 6-neurotransmitter transporter, dopamine-member 3 (SLC6A3). The dopamine receptor 2 (DRD2) is believed to play a role in the susceptibility to depression because of its role in the reward-mediating mesocorticolimbic pathways (Missale, Nash, Robinson, Jaber, & Caron, 1998). In particular, carriers of the A2/A2 allele appear to be vulnerable to depressive symptoms after stressful events (Opmeer, et al., 2010). Also, SLC6A3 gene and DRD4 have been found to be associated with high levels of depression (Lopez-Leon et al., 2008; Lopez Leon et al., 2005). These genes have also been associated with food intake. Specifically, DRD4 has been associated with reward-seeking behaviors, and one study has found an association between DRD4 (at least one 7 repeat) food cravings in response to food cues (Sobik, Hutchison, & Craighead, 2005). Also, the DRD2 gene has been associated with carbohydrate cravings (Noble, 2000; Noble et al.,

1994), increased sugar consumption (Eny, Corey, & El-Sohemy, 2009), and higher energy from fat (Barnard et al., 2009). Another gene, monoamine oxidase A (MAOA), that is associated with the production of an enzyme that metabolizes dopamine (in addition to serotonin and noradrenaline) has also been associated with mood and higher body mass index (Ducci et al., 2006; Fuemmeler et al., 2009). As it relates to food intake, a recent study in children found that the MAOAu-VNTR long allele compared with the short allele was associated with increased consumption of lipid-dense and sugar-dense foods (Galvão et al., 2011).

Notably, gender appears to be important in the relationships between depressive mood, food intake patterns, and dopamine related genes. As mentioned above, depression and intake of high fat and sucrose were more strongly associated in males from the project EAT cohort (Fulkerson, Sherwood, Perry, Neumark-Sztainer, & Story, 2004). Others have observed that while carbohydrate craving is more common in females (Drewnowski, 1995), the relationship with mood is stronger in men (Christensen & Pettijohn, 2001). Further, Eny et al. (2009) found that alleles of the DRD2 gene were associated differently in men and women with food intake patterns (esp., sugar intake). Depressive symptoms also have a different developmental course for female and male adolescents, emerging in early adolescence with higher severity in females (Hankin, 2009; Hankin et al., 1998; Wade, Cairney, & Pevalin, 2002). Thus, when examining associations between genetics and food intake patterns some have suggested that analyses should be conducted separately for men and women (Eny, et al., 2009).

Given that both depressive symptoms and genetic factors have been associated with food intake (esp., high calorie fat and sweet foods), and that food intake patterns and depressive symptoms appear to share common underlying genetic correlates, there may be potential synergies that occur with these two factors that influence food intake patterns. Individuals who are depressed may vary in the degree to which they seek out highly palatable foods based on underlying genetic differences. Such synergies are plausible given previous research in the smoking literature showing that smoking and nicotine dependence are heightened under conditions in which individual have certain dopamine-related gene alleles (e.g., DRD4 no 7 repeats, DRD2 any A1) and high depressive symptoms (Audrain-McGovern, et al., 2004; Lerman, et al., 1998).

The purpose of this study is to examine whether dopamine related polymorphisms predict food intake (esp., high calorie sweet and high calorie non-sweet foods) and the degree to which depressive symptoms might influence these associations. In this model, depressive symptoms exert influence on the genotype-food intake associations through both unique genetic and environmental pathways. Given that 1) previous research suggest associations between depressive symptoms and type of food intake (i.e., intake of sweet and high calorie foods), 2) the notably overlap in neurobiological mechanism underlying both depressive mood and intake of sweet and high calorie foods, we hypothesized that candidate genes associated with the regulation of dopamine would interact with depressive symptoms to predict high calorie sweet and high calorie non-sweet foods. We examined these associations separately for both males and females, given that gender appears to be important to these relationships. To explore the possibility that these genotypes associated with the dopamine and ultimately the rewarding properties of food might decrease intake of healthy foods, and these associations could be exacerbated by high levels of depression, we also evaluated associations with intake of low-calorie foods.

METHODS

Data Source

The study population was 20,745 adolescents from the National Longitudinal Study of Adolescent Health (Add Health), a nationally representative study of adolescents. The cohort includes respondents who completed in-home surveys on four separate occasions (April to December, 1995; April to August, 1996; August 2001 to August 2002; and January 2008–Feb 2009). The mean age of the participants in the four waves of data collection was 15.65 (SD = 1.75) years, 16.22 (SD = 1.64) years, 22.96 (SD = 1.77) years, and 28.9 (SD = 1.76) years, respectively. By design, the Add Health survey included a sample stratified by region, urbanicity, school type, ethnic mix, and size to garner a nationally representative sample. Precise details regarding the design and data collection have been described elsewhere (Resnick et al., 1997).

Study Sample

Although the Add Health is longitudinal, dietary data were only collected during Wave II. Buccal samples for DNA extraction were later collected on a subsample of participants during the Wave III data collection phase. Thus, for the purposes of this study, the sample was limited to respondent's data from Wave II for whom DNA data were available. A small proportion of the subsample of participants for whom DNA was collected included siblings. A random selection of unrelated individuals was sampled from this pool of participants yielding a study sample of 1551 unrelated participants.

Measures

Diet—The dietary data was derived from an in-home structured 24-hour questionnaire of food, drinks and snacks consumed the previous day. The questionnaire consisted of 55 food and beverage items that represented 76 variables on consumption and types (e.g. regular or low fat) (Boone-Heinonen J, 2008). The 55 variables were grouped to create three indices labeled as “high-calorie sweet”, “high-calorie non-sweet” and “low-calorie” foods. The categorization of food groups was developed to be similar to previous work by Jeffery et al. (2009) who investigated depressive symptoms and food intake in adult women. The high-calorie sweet food index consisted of foods such as chocolate candy, regular candy, cookies, doughnuts, and ice cream. Food listed on the high-calorie non-sweet index included regular meat, steak, fried chicken, fried fish, pizza, hot dogs, sausage, regular cheese, salad dressing, and whole milk. The low calorie food items included grilled chicken, grilled fish, low fat and skim milk, tofu, plain tuna fish and low fat yogurt. Scores were developed for each index and represent the average number of food and beverages consumed in a typical day. For the three indices, the means, standard deviations and ranges were: high-calorie sweets $M = 2.14$, $SD = 1.3$ (0 – 7); high-calorie non-sweet $M = 5.04$, $SD = 2.5$ (0 – 17); and low-calorie foods $M = 2.31$, $SD = 1.5$ (0 – 8). There were significant gender differences for each category, with males consuming higher quantities of food compared to females ($p < 0.001$) (data not shown).

Depressive Symptoms—The Add Health study included a modified 10-item version of the Center for Epidemiologic Studies – Depression (CES-D). The CES-D is frequently used measure of depressive symptoms in epidemiologic studies and has been used as both a continuous measure of depression or as a binary categorical measure indicating high severity of depressive symptoms. Cut-off scores have been used for categorization into severity subtypes, typically termed “non-depressed” and “mild to moderate depression” or, “at risk for depression” (Radloff, 1977). For Add Health, the response scale and tense (i.e., from the first to second person) of some CES-D items were modified, but have been shown to not meaningfully affect the internal structure of the measure (Crockett, Randall, Shen, Russell,

& Driscoll, 2005). Respondents are asked to indicate how often they experienced each depressive symptom in the past 7 days. An example of one of the items is “you felt depressed”. Responses range from 0 (never or rarely) to 3 (most of time or all of the time) with total scores ranging from 0 to 30. This version of the CES-D has demonstrated good internal consistency across waves (Cronbach’s $\alpha = .87$ at Wave III). For our analyses, individuals were classified into one of two groups, those reporting CES-D scores of 10 or greater and those reporting between 0 and 9 symptoms. We used a ≥ 10 point cutoff to categorize participants into high and low categories of depressive symptoms. This 10 symptom cutoff was chosen because previous literature has suggested that scores of ≥ 10 on a 10-item CES-D result in levels similar to those ≥ 16 on the full-length 20 item version (Andresen, Malmgren, Carter, & Patrick, 1994). Scores of this magnitude are indicative of the mild to moderate depressive symptoms category (Radloff, 1977).

Other Variables—Height and weight were measured by Add Health staff during an in-home interview. Body mass index (BMI) z scores were calculated using the Centers for Disease Control and Prevention SAS macro which computes age and gender adjusted standardized scores (“Centers for Disease Control and Prevention,”). Other covariates included indicators of socioeconomic status (e.g., parent-reported educational attainment), chronological age of participant, and self-identified race/ethnicity. Analyses were only conducted with American whites, African Americans, and Hispanics American participants. Native Americans and Asians were excluded from the analyses because they are underrepresented in the available data.

Genotyping—Buccal samples were collected on the participants and DNA extracted using a modification of procedures described previously (Freeman et al., 1997; Harris et al.; Lench, Stanier, & Williamson, 1988; Meulenbelt, Droog, Trommelen, Boomsma, & Slagboom, 1995; Spitz et al., 1998). In the Add Health data there are 6 genes that have been genotyped and are available for analysis. However, for this study only the 4 that are purportedly associated with dopamine regulation and availability were included in the analyses. The following were genotyped according to procedures described previously (Anchordoquy, McGeary, Liu, Krauter, & Smolen, 2003; Timberlake et al., 2006): the dopamine transporter (SLC6A3) gene (rs28363170), the Taq1A polymorphism of the dopamine D2 receptor (DRD2) gene (rs1800497), the dopamine receptor D4 (DRD4) gene (48-bp VNTR in exon 3), and a promoter of the monoamine oxidase A (MAOA) gene (30-bp VNTR). The genotypes were tested for deviations from Hardy Weinberg Equilibrium (HWE) and no deviations were observed ($p > .05$).

Statistical Analyses

Statistical analyses were conducted using SAS-callable SUDAAN (version 10.0.1) statistical software (Research Triangle Institute, 2001). SUDAAN controls for survey design effects of individuals clustered in sampling units by school and geographic region. Because gender differences have been found in severity of depressive symptoms (Hankin, 2009; Hankin et al., 1998; Wade, Cairney, & Pevalin, 2002) and in the relationship between genes and food intake (Eny, et al., 2009), analyses were conducted separately for males and females. However, to confirm that gender was relevant in this sample, a set of linear regression models predicting each of the 3 food categories with males and females combined were run testing for gender-by-depressive symptoms and gender-by-genotype interactions. Models included the covariates of adolescent age, parental educational level, race, and body mass index z score (BMI z score). When combining all subjects, we found significant gender-by-depressive symptoms and gender-by-genotype interactions when predicting high calorie sweet and high calorie non-sweet foods (all p s for interactions $< .05$, data not shown). The interactions were not statistically significant when the outcome was low-calorie foods.

However, the interaction p-values suggested a trend (all p-values for interactions $\leq .10$, data not shown). All of these above analyses were conducted with the SLC6A3, DRD2, and DRD4 genotypes. Since MAOA is located on the X chromosome it is common practice to analyze stratified by gender. It is noteworthy that males and females also differed in their average consumption of high-calorie sweet, high-calorie non-sweet and low-calorie foods (*males had higher mean scores*).

Next, a set of bivariate and multivariate analyses were conducted separately for each gender. For each of the 3 food categories, bivariate analyses were conducted to examine the mean differences in daily intake for each of the genes and for those high and low in depressive symptoms. In the first set of models (model 1) linear regression analyses were used to examine the association between depressive symptoms and genotype controlling for adolescent age, parental educational level, race, and body mass index z score (BMI z score). In a second set of models (model 2) an interaction (depressive symptom category-by-genotype) was added to the model. Interactions were deconstructed using a simple effect analysis which tested the influence of gene on food type stratified on high and low depression symptoms status. The Least Square Means (LS Mean) for average daily intake adjusted for race, age, parental education, and zBMI are reported for models in which significant interactions were found. For models testing the depressive symptom category-by-genotype interaction, the p-values from the test-statistic and the Benjamini-Hochberg False Discovery Rate (FDR) p-value are reported. This FDR p-value indicates statistical significance adjusted for multiple comparisons (Benjamini & Hochberg, 1995). In this case, an FDR p-value for 24 comparisons (3 outcomes, 4 models and 2 genders) with a threshold of .10 for significance was calculated and is presented along with the p-value for unadjusted for multiple comparisons.

RESULTS

Sample Characteristics

Table 1 displays the overall sociodemographics for the study population. The mean age of the sample was 16.6 (SD = 1.76) years. The majority of the sample was white with 52% female. Parental education level varied with a majority having some college or higher. Roughly, 22% of the sample reported CES-D scores ≥ 10 , which represented 25% and 17% of males and females, respectively.

Bivariate associations between categories of depressive symptom, genes and food intake

Table 2 displays bivariate associations between categories of depressive symptoms, genes and high-calorie sweet, high-calorie non-sweet and low-calorie foods for males and females. Females high in depressive symptoms reported consuming less of the low-calorie foods on a daily basis compared to females with low depressive symptoms ($p=0.01$). Males with DRD2 A2/A2 genotype reported consuming less of the high-calorie non-sweet foods than their counterparts with any A1 allele ($p=0.02$). All other associations between genes, depressive symptoms and food intake categories were not statistically significant.

Multivariate linear regression analyses

The results from the linear regression models (model 1) predicting high-calorie sweet, high-calorie non-sweet and low-calorie foods are shown in Table 3 for males and Table 4 for females. Controlling for BMI and other covariates, there were no significant main effects observed between the SLC6A3, DRD4 and MAOA genotypes predicting any of the food categories for males. Consistent with the bivariate analyses, the relationship between DRD2 and reported daily intake of high-calorie non-sweet foods remained significant ($p=0.04$). In the multivariate model for females, a significant main effects was observed between

SLC6A3 and reported daily intake of high-calorie sweet foods ($p=0.04$). No other significant associations were found between genotype and reported intake of the 3 food categories for females. Also consistent with the bivariate associations, depressive symptoms remained as a significant predictor of low-calorie food intake in the multivariate models. Additionally, females with high depressive symptoms had a higher average amount of daily intake of high-calorie sweet foods ($p=0.05$).

Genotype and Depression Symptoms Interaction Effects

The results of the interaction between genotype and depressive symptoms predicting high-calorie sweet, high-calorie non-sweet and low-calorie foods (model 2) are displayed in Table 3 for males and Table 4 for females.

For females there was a significant interaction between SLC6A3 and CES-D ($p=.002$, FDR $p=.004$). Analysis of this interaction effects indicates that among those with high depressive symptoms, those with the SLC6A3 10/10 allele reported greater intake of high-calorie sweet foods than their counterparts high in depressive symptoms with the SLC6A3 any 9 allele (LS mean 10/10 allele = 2.5, SE = .13; LS mean any 9 allele = 1.8, SE = .13, $p<.05$). There were no differences between carriers of the different alleles who were low in depressive symptoms (LS mean 10/10 allele = 1.9, SE = .08; LS mean any 9 allele = 1.9, SE = .08, $p>.05$) (Figure 1a).

For males, significant interactions were found between categories of depressive symptoms-by-DRD2 ($p=.021$ FDR $p=.008$) and categories of depressive symptoms-by-MAOA ($p=.029$, FDR $p=.013$) predicting intake of high-calorie non-sweet foods (Table 3). Post-hoc analysis of the depressive symptom-by-DRD2 interaction indicated that those high in depressive symptoms with the DRD2 any A1 reported significantly greater intake of high-calorie non-sweet foods than their counterparts with the A2/A2 allele (LS mean any A1 = 6.8, SE = .58; LS mean A2/A2 = 5.2, SE = .32, $p<.05$). Among those low in depressive symptoms, no significant difference were found between carriers of the different alleles (LS mean any A1 = 5.6, SE = .15; LS mean A2/A2 = 5.4, SE = .13, $p>.05$) (Figure 1b).

With respect to the interaction between MAOA and depression symptoms on high calorie non-sweet foods, the post-hoc analysis indicated that those with the low active MAOA allele and high depressive symptom reported significantly greater daily intake than their counterparts with high depressive symptoms and the MAOA active allele (LS Mean low active = 6.5, SE = .50; LS Mean active = 5.3, SE = .31, $p<.05$). For those low in depressive symptoms, no differences in intake were found between those with either the MAOA low active or active allele (LS Mean low active = 5.5, SE = .16; LS Mean active = 5.4, SE = .12, $p>.05$) (Figure 1c).

A significant interaction was also found between high depressive symptoms and DRD4 among males in the model predicting intake of low calorie foods ($p=.033$, FDR $p=.017$). The post-hoc analyses indicated that among males high in depressive symptoms, carriers of at least one 7 repeat allele reported consuming less low-calorie foods than their counterparts high in depressive symptoms with no 7 repeat alleles (LS mean at least on 7 repeat = 1.6, SE = .19; LS mean no 7 repeat = 2.3, SE = .18, $p<.05$). No differences were found between carriers of the two alleles who were low in depressive symptoms (LS mean at least on 7 repeat = 2.5, SE = .13; LS mean no 7 repeat = 2.4, SE = .07, $p<.05$) (Figure 1d).

DISCUSSION

The purpose of this study was to assess the association between dopamine genotype and food intake and potential interactions between depressive symptoms and genes putatively

related to dopamine regulation on reported intake of high-calorie sweet, high-calorie non sweet, and low-calorie foods. We were particularly interested in examining synergistic effects between depressive symptoms and genotypes on food intake patterns, since genotypes associated with food intake are similar to ones associated with mood regulation. Differences in these associations were examined with respect to gender. Among females, we found that those with high depressive symptoms reported lower intake of low calorie foods, but among males food intake was not associated with depressive symptoms. With respect to genotypes, there were significant associations between DRD2 and high-calorie non-sweet food intake among males and between SLC6A3 and high-calorie sweet food intake among females in adjusted models. Significant interactions between depressive symptoms and genotypes in predicting reported food intake were observed for polymorphisms in the DRD2, DRD4 and MAOA gene among males, and among females, the SLC6A3 gene. When applying the FDR method, only the SLC6A3 $\times$ CESD interaction predicting high-calorie sweet foods remained significant. However, we report interaction effects with low p-values, though insignificant using the FDR procedure, as they may be useful to future research. To our knowledge, this is the first evidence of a depressive symptom by gene interaction predicting reported food intake.

Our finding that females with high depressive symptoms reported higher intake of high-calorie sweet foods, but lower intake of low-calorie foods, is consistent with previous reports. In a sample of middle-aged women, Jeffery et al. (2009) also found that depressive symptoms were related to greater intake of high calorie sweet foods and revealed an association between depressive symptoms and reduced intake of low-calorie foods. Similarly, Mennella et al (2010) found that depression symptoms in children were associated with greater liking for sweet tasting foods and candies (Mennella, et al., 2010). Others have similarly shown that these individuals report greater consumption of high calorie foods (e.g. ready-to-eat and fast foods) (Liu et al., 2007) and high chocolate consumption (Rose, Koperski, & Golomb, 2010). In general, our findings examining depressive symptoms and intake of high calorie foods were in the expected direction. That is, those with higher depression did report slightly greater consumption of high calorie foods (both sweet and non-sweet) than those with low depressive symptoms, but these differences reached statistical significance for only females. Differences in measurement of food intake, samples and settings (laboratory vs. field settings) may account for some of these inconsistencies between our findings and extant literature.

In adjusted models, we found significant main effects for the association between DRD2 and SLC6A3 and reported food intake of high calorie foods. These associations differed by gender and type of high-calorie food (i.e., sweet and non-sweet). Specifically, we observed an association between DRD2 genotype and greater reported intake of high-calorie non-sweet foods in males. This finding is consistent with laboratory-based studies and studies with clinical samples that show associations with the DRD2 Taq1 A1 variant and consumption of carbohydrates (Noble, 2000), energy (Epstein et al., 2007), and fat intake (Barnard, et al., 2009). In females, we observed that those with the SLC6A3 10/10 genotype reported greater consumption of high-calorie sweet foods. In support of our findings, Pecina et al. (2003) examined elevated synaptic dopamine on spontaneous food and water intake and incentive motivation to obtain a palatable sweet reward in mutant DAT knockdown mice. The hyperdopaminergic mice had higher energy intakes and preference for a sweet reward than did the controls (Pecina, et al., 2003). We could not find studies that examined the interaction between depressive symptoms and dopamine related genotypes on food intake in human populations. However, studies have indicated that the DRD2 genotype was associated with higher calorie/energy intake and a potential association with food reinforcement (Epstein et al., 2002; Epstein et al., 2004); but the finding is not always

consistent (Epstein, et al., 2007). Continued research is needed to explore the association between DRD2 and SLC6A3 genotype and food intake.

We also found interactions between dopamine genotypes and depressive symptoms, which predicted food intake. Our findings suggested that for males, the combination of high depressive symptoms and either the DRD2 Taq1 A1 allele or the MAOA inactive variant was associated with the greatest intake of high-calorie non-sweet foods. Additionally, males with the DRD4 7 allele and high depression symptoms reported the lowest intake of low-calorie foods. However, when applying the FDR criterion for multiple testing, we cannot confirm that these interactions are statistically significant. However for females, the interaction between depressive symptoms and the SLC6A3 10/10 allele on intake of high-calorie sweet foods was statistically significant using this FDR criterion. Overall, these findings suggest that the degree to which depressive symptoms relate to food intake might be linked with individual genotype differences. The SLC6A3 gene codes for the dopamine transporter DAT1, which is believed to facilitate re-uptake of released dopamine back up into presynaptic terminals (Opmeer, et al., 2010). Alterations in SLC6A3 activity reflect changes in dopamine function (Mortensen & Amara, 2003) and binding affinity (Brunswick, Amsterdam, Mozley, & Newberg, 2003; Laasonen-Balk et al., 1999) which has been seen in depressed patients (Newberg, Amsterdam, & Shults, 2007). Individuals with depressive symptoms may consume higher amounts of highly palatable foods (e.g. high sugar and high fat) as a way of regulating dopamine availability and ultimately mood (Corsica & Pelchat, 2010; Rose, et al., 2010). Repeated stimulation of the reward pathways through highly palatable food may lead to dopamine dysregulation and overeating (Fulton, 2009). Further research is needed to confirm associations and to elucidate potential mechanisms.

The different effects we observed for males and females are noteworthy. Gender differences were found for the DRD2 genotype with males consuming less high-calorie non-sweet foods; *whereas* females with SLC6A3 10/10 genotype consumed higher amounts of high-calorie sweet foods. Additionally, we found significant gene-by-depression interactions that differed by sex. Gender differences in the dopaminergic system have also been documented in laboratory research with mice (Andresen, et al., 1994; Walker, Rooney, Wightman, & Kuhn, 2000) and in studies with human samples. A study examining whether genetic variation in the DRD2 gene affects habitual consumption of sugars found the highest sucrose intake among men who were homozygous for the CC allele; whereas women who were heterozygote's consumed the most sugars and CC homozygote's consumed the least (Eny, et al., 2009). These findings suggest that genetic variation in DRD2 can modulate sugar consumption differently in men and women. In the smoking literature, preliminary findings suggest gender differences in genetic variation in dopamine and sensitivity to nicotine in nonsmokers (Perkins et al., 2008). In particular, DRD4 and DRD2 variants are believed to modulate initial sensitivity to nicotine prior to the onset of dependence in men but not women (Perkins, et al., 2008). Taken together, the results highlight the importance of gender differences in dopaminergic activity that are related to dopamine genotype. Examining these differences can help us understand genetic variation in dopamine function and sensitivity. Further research is needed to confirm these findings.

To our knowledge, there are no studies that examined the interaction between dopamine genotype and depression symptoms on food intake or eating behaviors. Although these findings are encouraging and suggest that individual differences in food intake preference may be partially affected by depressed mood, continued research is needed before definitive conclusions can be made.

Limitations and Strengths

There are a number of limitations in this study. As with all candidate gene studies, findings may overestimate the modest, yet significant, effects reported here (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). To avoid overestimating the effects we used the Benjamini-Hochberg FDR, which is a method to correct for multiple comparisons while controlling the chance of false positives. It is essential to replicate these results before definitive conclusions can be made about the role dopamine related genes and depressive symptoms play on food intake. Add Health is a large longitudinal study with a sufficient sample for genetic studies. Although the sample was large, we were testing gene-behavior interaction effects, which reduced our sample size. Further evaluation of the effect of racial/ethnic groups by gender was not possible due to the limited sample size. Additionally, our analysis focused on one time point for which dietary data was collected (Wave II). Dietary data were not available in subsequent waves, thus, we cannot speculate on what effects dopamine genotype may have on future food consumption in this population. The use of a single 24-hour dietary recall, although administered in the home by a trained interviewer, is a limitation in this study. For an accurate assessment of dietary intake, repeat administrations are generally recommended (Schatzkin et al., 2003). We used a method of categorizing food types that was used by others so that comparisons of our results could be made with extant literature. In particular, our method of food categorization is consistent with Jeffery et al.,(2009) which focused on depressive symptoms and food intake (high-calorie sweet, high-calorie non-sweet and low-calorie food). However, replication studies in other samples that include robust dietary assessment measures are needed before definitive conclusions can be made.

Despite these limitations, our study has a number of strengths. We had a robust subsample of males and females with genetic data and were able to examine how depressive symptoms interact with dopamine related genes to influence food intake. Our finding suggests that dopamine polymorphisms may interact with depressive symptoms to influence food intake. Also, our findings indicated interesting gene-depression interactions that differed by sex. To our knowledge, this is the first study that investigated interactions between depressive symptoms and dopamine genotype on food intake. Future work examining genetics and psychological symptomatology as predictors of food intake patterns and quality are needed to confirm our findings.

Conclusion

In summary, we found a direct association for SLC6A3 gene and high-calorie sweet food intake and an interaction between depressive symptoms and SLC6A310/10 genotype with increased consumption *high-calorie sweet foods*. This association was found only in females. Our findings suggest genes that regulate dopamine may moderate the effects of depressive symptoms and influence the amount and type of food consumed. However, these findings are preliminary and need to be confirmed. The results underscore the need for additional research focused on understanding the role that specific genotypes may have on food intake in a large ethnically diverse sample of adolescents with depressive symptoms. This research has important public health implications. We live in an obesogenic environment where exposure to high energy-dense foods is widely available. Depressed adolescents with certain other risk factors (e.g., specific genotypes) may be more susceptible to consuming greater quantities of foods high in refined carbohydrates. Targeted dietary intervention studies focused on this population are needed to prevent obesity and chronic disease later in life.

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Highlights (Core Findings)

- Males with DRD2 genotype reported higher intakes of high-calorie non-sweet foods
- Females with SLC6A3 genotype reported higher intakes of high-calorie sweet foods
- Females with high depressive symptoms and the SLC6A3 10/10 allele reported greater intake of high-calorie sweet foods than their counterparts high in depressive symptoms with the SLC6A3 any 9 allele.

Figure 1.
Interaction between genotype and depression on average number of high-calorie sweet, high-calorie non-sweet and low calorie foods

Table 1

Characteristics of study sample.

	N	%
Gender		
Male	748	48.2
Female	803	51.7
Ethnicity		
White	1021	65.8
Hispanic	280	18.0
Black	250	16.1
Parental Education Level		
Less Than High School	162	11.7
High School or Equivalent	384	27.8
Some College	410	29.7
College or Higher	427	30.9
BMI Category for Age and Gender		
Underweight (< 5th percentile)	63	4.45
Normal Weight (5th – 85th percentile)	992	70.1
Overweight (85th – 95th percentile)	186	13.1
At Risk for Overweight (> 95th percentile)	175	12.4
	<i>Mean</i>	<i>SD</i>
Age (range 13 – 21 years)	16.6	1.69

Table 2

Bivariate association between categories of depressive symptoms and genotype on average number of high-calorie sweet, high-calorie non sweet, and low-calorie foods per day

	Males				Females			
	high-calorie sweet		high-calorie non-sweet		high-calorie sweet		high-calorie non-sweet	
	<i>M (SE)</i>	<i>p value</i>	<i>M (SE)</i>	<i>p value</i>	<i>M (SE)</i>	<i>p value</i>	<i>M (SE)</i>	<i>p value</i>
CESD								
Low < 10	2.29 (.07)		5.55 (.13)	2.52 (.09)	1.90 (.08)		4.48 (.12)	2.35 (.09)
High ≥ 10	2.39 (.18)	0.61	6.21 (.73)	0.36	2.05(.17)	0.30	4.80 (.43)	1.98 (.11)
DRD2								
Any A1	2.33 (.10)		5.99 (.27)	2.52 (.13)	1.95 (.11)		4.62 (.20)	2.16 (.11)
A2/A2	2.32 (.08)	0.96	5.38 (.18)	0.02	1.93 (.10)	0.85	4.53 (.18)	2.32 (.09)
SLC6A3								
Any 9	2.29 (.10)		5.59 (.28)	2.47 (.17)	1.90 (.13)		4.47 (.20)	2.25 (.12)
10/10	2.37 (.08)	0.55	5.62 (.21)	0.94	1.97 (.09)	0.59	4.59 (.17)	2.22 (.12)
DRD4								
One 7	2.36 (.12)		5.75 (.02)	2.52 (.16)	1.99 (.13)		4.47 (.20)	2.21 (.14)
No 7	2.31 (.08)	0.79	5.59 (.23)	0.57	1.91 (.08)	0.49	4.63 (.17)	2.29 (.09)
MAOA								
Inactive	2.17 (.10)		5.81 (.22)	2.41 (.13)	2.00 (.10)		4.67 (.22)	2.28 (.11)
Active	2.42 (.09)	0.08	5.52 (.24)	0.33	1.85 (.11)	0.19	4.41 (.15)	2.23 (.09)

Table 3

Multivariate association for main effects models and additive effect between gene and depression for males

	high-calorie sweet			high-calorie non sweet			low-calorie		
	Estimate	(se)	p-value	Estimate	(se)	p-value	Estimate	(se)	p-value
SLC6A3									
Model 1 (main effects)									
Intercept	3.43	(0.60)		7.16	(1.24)		3.71	(0.67)	
SLC6A3									
any 9									
10/10	-0.04	(0.11)	0.70	0.15	(0.20)	0.47	-0.05	(0.13)	0.71
CESD									
Low (< 10)									
High (≥ 10)	-0.06	(0.20)	0.78	0.10	(0.37)	0.78	-0.18	(0.15)	0.23
Model 2 (main effects and interaction)									
SLC6A3 $\times$ CESD	0.38	(0.33)	0.26	-0.34	(0.63)	0.59	0.39	(0.31)	0.20
DRD2									
Model 1 (main effects)									
Intercept	3.38	(0.57)		7.54	(1.24)		3.31	(0.67)	
DRD2									
Any A1									
A2/A2	-0.05	(0.09)	0.61	-0.41	(0.20)	0.04	0.02	(0.14)	0.88
CESD									
Low (< 10)									
High (≥ 10)	0.02	(0.19)	0.91	0.29	(0.37)	0.44	-0.22	(0.15)	0.14
Model 2 (main effects and interaction)									
DRD2 $\times$ CESD	0.02	(0.33)	0.95	-1.64	(0.71)	0.02	-0.07	(0.31)	0.81
DRD4									
Model 1 (main effects)									
Intercept	3.40	(0.57)		7.92	(1.28)		3.42	(0.65)	
DRD4									
one 7 repeat									
no 7 repeat	-0.14	(0.06)	0.36	-0.04	(0.23)	0.86	0.07	(0.13)	0.58

	high-calorie sweet			high-calorie non sweet			low-calorie		
	Estimate	(se)	p-value	Estimate	(se)	p-value	Estimate	(se)	p-value
CESD									
Low (< 10)									
High (>= 10)	0.02	(0.19)	0.91	0.28	(0.37)	0.44	-0.23	(0.14)	0.11
Model 2 (main effects and interaction)									
DRD4 × CESD	0.15	(0.35)	0.66	0.18	(0.78)	0.82	0.68	(0.32)	0.03
MAOA									
Model 1 (main effects)									
Intercept	2.37	(0.22)		6.19	(0.42)		2.26	(0.23)	
MAOA									
Inactive									
Active	0.02	(0.12)	0.85	-0.28	(0.20)	0.18	0.01	(0.12)	0.94
CESD									
Low (< 10)									
High (>= 10)	-0.01	(0.19)	0.97	0.24	(0.36)	0.51	-0.24	(0.15)	0.10
Model 2 (main effects and interaction)									
MAOA × CESD	-0.16	(0.29)	0.59	-1.39	(0.64)	0.03	-0.49	(0.36)	0.17

Note: Model 1 controls for maternal education, age, race/ethnicity, and BMI z score. Model 2 controls for maternal education, age, race/ethnicity, BMI z score, main effect of gene, and main effect of depressive symptom category

Table 4

Multivariate association for main effects models and additive effect between gene and depression for females

	high-calorie sweet			high-calorie non sweet			low-calorie		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
SLC6A3									
Model 1 (main effects)									
Intercept	3.65	(0.51)		8.21	(0.91)		4.17	(0.64)	
SLC6A3									
any 9									
10/10	0.18	(0.09)	0.04	-0.04	(0.17)	0.83	0.11	(0.11)	0.34
CESD									
Low (< 10)									
High (>= 10)	0.21	(0.11)	0.05	0.19	(0.28)	0.49	-0.40	(0.11)	0.00
Model 2 (main effects and interaction)									
SLC6A3 × CESD	0.73	(0.24)	0.00	0.44	(0.49)	0.36	0.04	(0.30)	0.91
DRD2									
Model 1 (main effects)									
Intercept	3.71	(0.51)		7.95	(0.91)		4.25	(0.64)	
DRD2									
Any A1									
A2/A2	0.01	(0.09)	0.93	0.03	(0.17)	0.88	-0.01	(0.12)	0.94
CESD									
Low (< 10)									
High (>= 10)	0.18	(0.11)	0.10	0.23	(0.28)	0.42	-0.41	(0.11)	0.00
Model 2 (main effects and interaction)									
DRD2 × CESD	-0.09	(0.26)	0.72	0.63	(0.40)	0.11	-0.19	(0.25)	0.44
DRD4									
Model 1 (main effects)									
Intercept	3.75	(0.51)		7.94	(0.92)		4.23	(0.62)	
DRD4									
one 7 repeat									
no 7 repeat	-0.02	(0.09)	0.85	0.15	(0.15)	0.33	-0.04	(0.11)	0.75

	high-calorie sweet			high-calorie non sweet			low-calorie		
	<i>Estimate</i>	<i>SE</i>	<i>p-value</i>	<i>Estimate</i>	<i>SE</i>	<i>p-value</i>	<i>Estimate</i>	<i>SE</i>	<i>p-value</i>
CESD									
Low (< 10)									
High (>= 10)	0.18	(0.11)	0.10	0.23	(0.28)	0.41	-0.40	(0.11)	0.00
Model 2 (main effects and interaction)									
DRD4 × CESD	-0.01	(0.23)	0.96	-0.08	(0.50)	0.88	-0.29	(0.22)	0.19
MAOA									
Model 1 (main effects)									
Intercept	2.28	(0.14)		4.23	(0.36)		2.44	(0.22)	
MAOA									
Inactive									
Active	-0.12	(0.10)	0.24	-0.15	(0.15)	0.29	-0.54	(0.11)	0.62
CESD									
Low (< 10)									
High (>= 10)	0.20	(0.11)	0.07	0.25	(0.29)	0.40	-0.38	(0.12)	0.00
Model 2 (main effects and interaction)									
MAOA × CESD	0.11	(0.23)	0.63	0.36	(0.45)	0.42	-0.10	(0.28)	0.72

Note: Model 1 controls for maternal education, age, race/ethnicity, and BMI z score. Model 2 controls for maternal education, age, race/ethnicity, BMI z score, main effect of gene, and main effect of depressive symptom category